



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-D-1692]

Elemental Impurities in Drug Products; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Elemental Impurities in Drug Products."

This draft guidance provides recommendations regarding the control of elemental impurities of human drug products marketed in the United States consistent with implementation of International Council for Harmonisation (ICH) guidance for industry "Q3D Elemental Impurities." This draft guidance will also assist manufacturers of compendial drug products in responding to the issuance of the United States Pharmacopeia (USP) requirement for the control of elemental impurities.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-D-1692 for Elemental Impurities in Drug Products. Received comments will be placed in the docket and,

except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION". The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the

prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: John Kauffman, Center for Drug Evaluation and Research (HFD-920), Food and Drug Administration, 645 S. Newstead Ave., St. Louis, MO 63110, 314-539-2168; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Elemental Impurities in Drug Products." This draft guidance provides recommendations regarding the control of elemental impurities of human drug products marketed in the United States consistent with implementation of ICH Q3D. The draft guidance will also assist manufacturers of compendial drug products in responding to the issuance of the USP requirement for the control of elemental impurities.

USP introduced new limits and analytical procedures for elemental impurities in General Chapters <232> Elemental Impurities - Limits and <233> Elemental Impurities - Procedures. Their primary goals are to (1) set limits for acceptable levels of elemental impurities in finished drug products, and (2) update the methodology used to test for elemental impurities in drug products to include modern analytical procedures. ICH Q3D contains recommendations for manufacturers of human drugs and biologics on applying a risk-based approach to control elemental impurities and permitted daily exposure. USP worked closely with ICH to align its new General Chapters with ICH Q3D.

Because elemental impurities pose toxicological concerns and do not provide any therapeutic benefit to the patient, their levels in drug products should be controlled within acceptable limits. In general, FDA recommends that the manufacturer of any U.S. marketed drug product follow ICH Q3D recommendations to establish appropriate procedures for identifying and controlling elemental impurities in the drug product based on risk assessment and product-specific considerations, unless the drug product must comply with USP–NF requirements. This draft guidance outlines approaches for implementation of USP <232>, <233>, and ICH Q3D in new and existing products.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on elemental impurities in drug products. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

## II. The Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 314 for submitting NDAs and ANDAs, including supplemental applications and annual reports, have been approved under OMB control number 0910-0001. The collections of information in 21 CFR part 211 and part 212 (CGMPs) have been approved under OMB control numbers 0910-0139 and 0910-0667.

### III. Electronic Access

Persons with access to the Internet may obtain the document at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, or <http://www.regulations.gov>.

Dated: June 27, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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